

REMARKS

Claims 2-4, 6-7, 10, and 16-29 are pending. Claims 22-33 are newly added. Support for newly added Claims 22-33 is found throughout the specification; for example see Figures 2 and 3, the specification at page 18, line 22 through page 20, line 21; page 6, lines 1-3; page 12, lines 14-15, and page 17, lines 22-24.

As a preliminary matter, the paragraph beginning at page 12, line 7 has been amended to correct an obvious error in the recitation of fluorescent lanthanide metal ions, i.e., the non-fluorescent lanthanide metal ion Er has been replaced by the fluorescent lanthanide metal ion Eu.

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction.

In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

Applicants submit that a person skilled in the art would recognize that Er is a non-fluorescent metal ion and that the appropriate correction would be to replace Er with Eu, a fluorescent metal ion. Accordingly, applicants submit that this amendment is not new matter and respectfully request entry of the amendment.

Objections to the Meade Declaration

The Patent Office cites Goodman and Kochetkov et al. to support their view that the term “anhydronucleosides” is well known in the prior art to encompass a much larger subject matter area than Prof. Meade’s declaration suggests. Thus, in Patent Office’s view, applicants have given the term “anhydronucleosides” a meaning that is repugnant to the usual meaning of that term. *See* Office Action, page 2. Applicants respectfully disagree.

The term “anhydronucleosides” is defined in the specification at page 18, line 22 through page 21, line 13, as follows:

By “anhydro-nucleoside” herein is meant a 2,2’-, 2,3’- or 2,5’ anhydronucleoside, comprising an oxygen bridge between the C-2 of the base pyrimidine and the C-2’ or C-3’ of the ribose or ribose analog. See for example Sebesta et al., Tetrahedron 52:14385 (1996); McGee et al., J. Org. Chem. 61:779 (1996); Fox et al., Advances in Carbohydrate Chemistry 14:283 (1959); Codington et al., J. Org. Chem. January 1962, pages 163-167; Glinski et al., J. Org. Chem. 38:4299 (1973); Kirschenheuter et al., Tetrahedron Lett. 35:8517 (1994); Mengel et al., Angew. Chem. Int. Ed. Engl. 17:525 (1978); Miller et al., 29:1772 (1964); and references cited therein, all of which are expressly incorporated by reference. In some cases, as is generally outlined in Moffatt, Transformations of the Sugar Moiety of Nucleosides, pp71-164, hereby expressly incorporated by reference, anhydronucleosides of purines can be made, forming a bridge between the N-3 of the purine and the 2’, 3’ or 5’ position on the ribose. As will be appreciated by those in the art, anhydronucleosides can be made with all the bases, and many base analogs. This is done as is well known in the art; see Moffatt, supra, Sebesta, supra, and McGee, supra.

This definition meets the requirements of §112, ¶2, because:

The requirement that the claims “particularly point[] out and distinctly claim[]” the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification. “If the claims when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more.” *Miles Laboratories, Inc. v. Shandon*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126(Fed. Cir. 1993); see also *Union Pacific Resources Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692, 57 USPQ2d 1293, 1297(Fed. Cir. 2001); *North American Vaccine, Inc. v. American Cyanamid Co.*, F.3d 1571, 1579, 28 USPQ2d 1333, 1339(Fed. Cir. 1993); *Hybritech, Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95(Fed. Cir. 1986).

See *S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1371-72 (Fed. Cir. 2001).

Dr. Meade’s declaration supports the view that a person experienced in the field of the invention would understand the meaning of the term “anhydronucleosides” when read in light of the specification. Prof. Meade’s view is not contrary to that of a person skilled in the art, as a number of scientific papers were enclosed with Dr. Meade’s declaration (i.e. Exhibits 12, 16, 17,

18, 21-24), that refer to anhydronucleosides as comprising an oxygen bridge between the C-2 of the base pyrimidine and C-2' or C-3' of the ribose or purine nucleosides that have an oxygen bridge between the C-8 of the purine residue and a hydroxyl group, e.g., C-2' or C-3' of the ribose. *See* response filed May 20, 2003.

Moreover, assuming, *arguendo*, that the Patent Office's assertion that the meaning given to "anhydronucleosides" is repugnant to the usual meaning of that term, Applicants respectfully direct the Patent Office's attention to M.P.E.P § 2173.05(a) which states that:

Consistent with the well-established axiom in patent law that a patentee or applicant is free to be his or her own lexicographer, a patentee or applicant may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings if the written description clearly redefines the terms.

See, e.g., Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999); *see also, Hormone Research Foundation Inc. v. Genentech Inc.*, 9004 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990) ("While we have held many times that a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning," in such a situation the written description most clearly redefine a claim term "so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term.").

In any event, in the interests of furthering the prosecution in this case, without agreeing to the Examiner's premise and retain the right to pursue claims with this term in further cases, the claims have all been amended to include the phrase "2'" or "3'" or both.

Accordingly, Applicants submit that the meaning of "anhydronucleosides" when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention.

Objections to the Specification

The Patent Office lists a number of pages in the specification where references are cited. It is the Patent Office's belief that Applicants are attempting to incorporate essential material via these citations. *See* Office Action at page 3. Applicants respectfully disagree that these references contain essential material as defined in M.P.E.P. § 608.01(p) I.A.

“Essential material” is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention or (3) describe the best mode (35 U.S.C. 112).

Applicants invention is directed to methods of synthesizing modified nucleic acids comprising signalling moieties. Thus, the specification describes a general synthetic scheme comprising reacting an anhydro-nucleoside with a primary amine or an electron transfer moiety with a primary amine in the presence of an activation agent. This general synthetic scheme can be used to: 1) add one or more ligands followed by the addition of a metal ion; 2) add a transition metal chelated by one or more ligands; and 3) add a metallocene such as ferrocene. However, the various components used to make the modified nucleosides (i.e., nucleosides, nucleotides, nucleic acid analogs, ligands, electron transfer moieties, etc.), are known to a person of skill and thus, fall within the definition of “nonessential subject matter”.

“Nonessential subject matter” is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art. *See* M.P.E.P. § 608.01(p) I.A. M.P.E.P. § 608.01(p) I.A. allows nonessential material to be incorporated by reference. Incorporation of nonessential subject matter may be done by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications.

The material incorporated by reference is nonessential subject matter and is cited for the purpose of illustrating the state of the art. For example, the references to patents and other publications at pages 4 and 5 is used to illustrate that the various nucleic acid analogs that may

be used in the invention are known to those of skill in the art. Similarly, the references to prior filed, commonly owned U.S. applications on page 7 is used to illustrate that the use of electron transfer moieties as signalling moieties are known to those of skill in the art. The references cited on pages 9, 10, 14 are used to illustrate that suitable co-ligands and chelates for chelating transition metals are known to those of skill in the art. The references cited on page 12 are used to illustrate that suitable optical dyes for use as signalling moieties are known to those of skill in the art. The references cited on page 19 are used to illustrate that Applicants definition of “anydronucleoside” i.e., a “2,2’-, 2,3’- or 2,5’ anydronucleoside, comprising an oxygen bridge between the C-2 of the base pyrimidine and the C-2’ or C-3’ of the ribose or ribose analog” is not is not repugnant to the usual meaning of the term. The references cited on page 21 are used to illustrate that the modified nucleosides made according to the synthetic scheme disclosed in the specification can be incorporated into a growing oligonucleotide. The reference cited on page 26, line 7 are used to illustrate that if the modified nucleic acids are made comprising an MRI agent they can be used as known in the art. The use of “all references cited herein are incorporated by reference in their entirety” at page 26, lines 11-12, is commonly used to ensure that all references cited within the body of the specification are incorporated by reference. Applicants note that U.S. Patent No. 6,020,475, examined by Examiner Crane, also uses this language. As the practice of incorporation by reference has not been used to incorporate essential material, Applicants request withdrawal of the objection.

The specification has been checked for typographical errors and corrected where necessary. Accordingly, the amendments do not present new matter.

Applicants respectfully request withdrawal of the objections.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2-3, 7, 10 and 16-21 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Patent Office states that the deletion of the term “further comprising” renders Claims 2 and 3 lacking in proper antecedent basis because the claim from which they depend does not specify the added subject matter of these claims. See Office Action page 4. Applicants respectfully disagree. In the interests of furthering prosecution, the term has been reintroduced.

The Patent Office has reiterated its rejection of Claims 2 and 3, for lacking steps involved in the process of adding phosphoramidite groups and phosphoramidite-derivatized nucleosides to the terminus of a growing oligonucleotides chain. According to the Patent Office, the *only* way to remove the indefiniteness rejection is to provide chemical structures for the starting material, the intermediate products, and the products. See Office Action, pages 4-5.

Applicants reiterate their position that a person of ordinary skill in the art would know the steps involved in the process of adding phosphoramidite groups and phosphoramidite-derivatized nucleosides to the terminus of a growing oligonucleotide chain.

As argued in the Response to Office Action mailed May 20, 2003, and summarized herein for completeness, Applicants presented several articles in support of their position that the process of adding phosphoramidite groups and phosphoramidite-derivatized nucleosides to the terminus of a growing oligonucleotides chain would be well known to a person of ordinary skill in the art. Applicants noted in their response to Office Action mailed May 20, 2003, that none of cited references provided a detailed description for the addition of a phosphoramidite moiety to a nucleoside or incorporation of the phosphoramidite modified nucleoside into an oligonucleotide. Instead, the above references refer the reader to established procedures for the preparation of DMT protected nucleoside phosphoramidites and subsequent oligonucleotide synthesis. For example, Meade and Kayyem state that a DMT-2'-N-trifluoroacetyl-protected phosphoramidite of

2'-amino-2'-deoxyuridine was prepared by variation of published procedures and reference Yamaguchi and Hirao (1983) 24:391 and that oligodeoxyribonucleotides were assembled by standard solid phase automated DNA synthesis techniques referencing Kline, et al. (1990) J. Am. Chem. Soc., 112:7373; Nibonowicz and Pardi (1992) Nature, 355:184; Batey, et al., (1992) Nucleic Acids Res., 20:4515; Michnicka, et al. (1993) Biochemistry, 32:395; Quant, et al. (1994) Tetrahedron Lett., 35:6649 (see Exhibit 13).

The specification at page 21, line 1-22 also outlines general methods for converting a modified nucleoside into the phosphoramidite form.

Finally, Applicants again refer the Patent Office to paragraph 8 of Dr. Meade's declaration, in which Dr. Meade states that oligonucleotide synthesis using phosphoramidite chemistry involves a series of deprotection, coupling, capping, and oxidation steps that are repeated until the specified nucleotide chain is constructed. The details of which are set forth in standard reference books such as Gait, M., ed. (1984) *Oligonucleotide Synthesis: A Practical Approach*, Oxford University Press, Oxford, and Eckstein, F., ed. (1991) *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press, Oxford.

As can be seen from the above discussion, a person of ordinary skill in the art would know the steps required for adding a phosphoramidite group to a modified nucleoside and for adding a phosphoramidite-derivatized nucleoside into a growing oligonucleotide chain. Applicants respectfully request withdrawal of the rejection of Claims 2 and 3 under 35 U.S.C. § 112, second paragraph.

The Patent Office states that Claim 3 is a "use" claim and thus, is indefinite for failing to recite a positive step delimiting how the use is practiced. *See Office Action* at page 6. Applicants respectfully disagree.

Claim 3 discloses a method for incorporating a 2'-modified nucleoside comprising a phosphoramidite group at 3' position into a nucleic acid. Applicants respectfully submit that Claim 3 discloses a "method" and is not a "use" claim as defined in M.P.E.P. § 2173.05(q). As the incorporation of this moiety into a growing nucleic acid chain is well known in the art, Applicants submit that it is not necessary to set forth additional steps in the process and respectfully request withdrawal of the rejection.

The Patent Office states that the use of the terms "cyclization agent" and "cyclized intermediate" in Claim 7 "are relatively meaningless unless details of the chemical reaction being alluded to are provided". See Office Action at Page 7.

Applicants respectfully submit that the use of the terms "cyclization agent" and "cyclized intermediate" in Claim 7 "meet the requirements of §112, ¶2 as set forth below:

The requirement that the claims "particularly point[] out and distinctly claim[]" the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification. "If the claims when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more." *Miles Laboratories, Inc. v. Shandon*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126(Fed. Cir. 1993); see also *Union Pacific Resources Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692, 57 USPQ2d 1293, 1297(Fed. Cir. 2001); *North American Vaccine, Inc. v. American Cyanamid Co.*, F.3d 1571, 1579, 28 USPQ2d 1333, 1339(Fed. Cir. 1993); *Hybritech, Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95(Fed. Cir. 1986).

See *S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1371-72 (Fed. Cir. 2001).

As argued in the Response to Office Action mailed May 20, 2003, and summarized herein for completeness, "cyclization agent" and "cyclized intermediate" are art recognized terms. For example, see Exhibits 9, 10, 11, and 12, enclosed with the Response to Office Action mailed May 20, 2003. Additional support for , "cyclization agent" and "cyclized intermediate"

being art recognized terms is found in Dr. Meade's declaration, enclosed with the Response to Office Action mailed May 20, 2003.

Finally, page 20, lines 12-17 of the specification for a definition of "cyclization agent". Applicants submit that the definitions provided for "cyclization agent" and "cyclized intermediates", meet the requirements of § 112, paragraph 2 and respectfully request withdrawal of the rejection.

The Patent Office has rejected Claim 7 the term "an electron transfer moiety" is indefinite functional language. *See* Office Action page 7.

In Ex parte Benning, Emte, Grosskinshky and Fruhbuss, 128 USPQ (B.P.A.I. 1960) the Claims were rejected as "functional, indefinite and unduly broad" because they included "at a temperature sufficiently high to oxidize" and "until a substantially chlorine-free reaction product is formed". This rejection was not sustained because "the noted expressions, when considered in their context, adequately identify the temperature and time conditions for the first stage of the reaction."

The specification provides both a definition and a description of what Applicant means by "electron transfer moiety". The definition of "electron transfer moiety" is found in the specification at page 7, lines 13-25 and specific electron transfer moieties for use in the methods of the present invention are disclosed in the specification; for example see page 8, lines 1-10; and page 11, lines 10-23.

Applicants respectfully contend that the provided description for "electron transfer moiety" clearly and definitely sets forth what is meant by electron transfer moiety within the scope of the invention and request withdrawal of the rejection.

The Patent Office rejects Claim 10 for using words that merely "hint at the structure of the intended product". *See* Office Action at page 8. For example, the Patent Office finds that

the use of the following terms are indefinite: “comprising”; “covalently attached polydentate ligand that chelates a transition metal”. Applicants respectfully disagree.

The transitional term “comprising”, which is synonymous with “including”, “containing”, or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

See, e.g., Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) (“Comprising” is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) (“comprising” leaves “the claim open for the inclusion of unspecified ingredients even in major amounts”).

Recitation of the transitional phrase “comprising” in Claim 10 leaves Claim 10 open for the inclusion of unspecified ingredients, such as the base comprising the anhydronucleoside, the type of the ligand, and the transition metal ion. Applicants respectfully request withdrawal of the rejection.

The definiteness requirement of § 112, paragraph 2 “focuses on whether the claims, as interpreted in view of the written description, adequately perform their function of notifying the public of the [scope of the] patentee’s right to exclude.” *See S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1371-72 (Fed Cir. 2001). Thus, the definiteness requirement of § 112, paragraph 2, requires “that the language employed be analyzed, not in vacuum, but always in light of teachings of prior art and of particular application disclosure as it would be interpreted by one possessing ordinary level of skill in pertinent art.” *See In re Johnson and Farnham*, 194 USPQ 187 (CCPA 1977).

In their Response to Office Action mailed May 20, 2003, portions of which are reiterated herein for the sake of completeness, Applicants provided exhibits from scientific journals and the declaration of Dr. Meade to support their position that the language used in the Claim 10, as well as the other pending claims, were art recognized terms and thus, that a person possessing ordinary skill in the art would understand the metes and bounds of the pending claims.

Moreover, Applicants note that references in a claim to art recognized terms that encompass a large number of compounds do not make a term indefinite and of uncertain scope provided that a person of skill in the art would not be confused as to subject matter encompassed by the claim. *See, for example, In re Skoll*, 187 USPQ 481 (CCPA 1975) (Although there are undoubtedly a large number of acids which come within the scope of “organic and inorganic acids,” the expression is not for that reason indefinite. We see no reason to believe that the public would be confused as to what *subject matter* is circumscribed by appellant’s claim.); *see also Ex parte Scherberich and Pfeifer*, 201 USPQ 397 (B.P.A.I. 1997) (Even though the sole limitation on the basic nitrogen compound, that it have “at least a hydrogen atom attached to the basic nitrogen atom,” provides for an extensive group of amines, we see no reason that those skilled in the art would be confused by such a description or that they would not be able to determine with a reasonable degree of accuracy the subject matter circumscribed by the definition. As to the term “aryl” it is recognized that various authorities may place a slightly different interpretation on its meaning; however, when used as here in conjunction with the terms “aralkyl” and alkaryl” we are of the opinion that those in the art readily appreciate the total scope of the subject matter being defined. Irrespective of whether the term “aryl” is restricted to an “organic radical derived from an aromatic hydrocarbon by the removal of one atom; e.g., phenyl from benzene, or could be read as inclusive of the tolyl radical ($\text{CH}_3\text{C}_6\text{H}_4\text{M}$), it is believed

apparent that the claims' use of the three terms "aryl," "aralkyl," and "alkaryl" clearly indicates the intended scope of the substituent groups.).

Accordingly, Applicants submit that language used in Claim 10 does not render Claim 10 indefinite, because the meaning and scope of the claim when viewed in light of the specification by a person of ordinary skill in the art would be apparent, and request withdrawal of the rejection.

The Patent Office rejects Claim 17 and 18 because the "oxidation state" of the metals in Claim 17 and "donor atom" in Claim 18 is not defined. Applicants respectfully disagree.

As argued above, if the meaning and scope of the claim when viewed in light of the specification by a person of ordinary skill in the art is apparent, the Claim is not indefinite. Applicant submits that a person of ordinary skill would know the appropriate oxidation state of the metal for use with a given chelate. In the Response to the Office Action mailed May 20, 2003, Applicants provided several Exhibits to illustrate that a person of skill in the art would be able to select an appropriate ligand based on the choice of metal ion.

Moreover, these Exhibits also illustrate that a person of skill in the art would understand what is meant by a "donor atom" when used in conjunction with a transition metal. Accordingly, Applicants submit that Claims 17 and 18 meet the requirements under § 112, paragraph 2 and and respectfully request withdrawal of the rejection.

The Patent Office rejects Claims 16, and 19-21 for using the terms "ferrocene" "pyridine", "bipyridine" and phenanthroline" because each term is directed to a separate chemical compound and not a substituent group. See Office Action at page 10.

Claims 16, and 19-21 disclose species of electron transfer moieties or polydentate ligands. Claim 16 is directed towards a species of electron transfer moiety, i.e., ferrocene. Similarly, Claims 19-21 disclose species of polydentate ligands comprising a primary amine and

one or more ligands, i.e., “pyridine,” “bipyridine,” and phenanthroline”. The disclosure of these compounds as species of electron transfer moieties or as ligands is consistent with the disclosure in the specification. For example, at page 7, lines 16-18, describe an electron transfer moiety as a molecule that loses or accepts an electron under certain conditions. The specification then goes on to disclose ferrocene as being capable of electron transfer. See specification at page 10, lines 9-16. Similarly, species of ligands are disclosed in the specification beginning at page 8, line 11 through page 9, line 17.

Moreover, assuming, *arguendo*, that the Patent Office’s assertion that each term is directed to a separate chemical compound and is thus technically incorrect, Applicants respectfully direct the Patent Office’s attention to M.P.E.P § 2173.05(a) which states that:

Consistent with the well-established axiom in patent law that a patentee or applicant is free to be his or her own lexicographer, a patentee or applicant may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings if the written description clearly redefines the terms.

See, e.g., Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999); *see also, Hormone Research Foundation Inc. v. Genentech Inc.*, 9004 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990) (“While we have held many times that a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning,” in such a situation the written description most clearly redefine a claim term “so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term.”).

Applicants submit that the specification clearly defines “ferrocene” “pyridine”, “bipyridine” and phenanthroline” as species of electron transfer moieties or ligands such that those skilled in the art would be appraised of the scope of the invention. Accordingly, Applicants request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 2-11 and 13-15 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Specifically, claims 7 and 10 are rejected for the use of the generic terms such as “anydro-nucleoside” and “modified nucleoside”.

An objective standard for determining compliance with the written description requirement is “does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.

See *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

As argued above and in response to the Office Action mailed May 20, 2003, terms such as “anydro-nucleoside”, “modified nucleoside”, etc. are art recognized terms and thus can be used without further definition.

Definitions for “anydronucleosides,” “modified nucleoside,” and “activated anhydronucleoside” are provided in the specification. For example, “anydronucleoside” is defined as a “2,2’-, 2,3’- or 2,5’ anydronucleoside, comprising an oxygen bridge between the C-2 of the base pyrimidine and the C-2’ or C-3’ of the ribose or ribose analog.” See specification at page 18, line 23 through page 19, line 13. An “activated anhydronucleoside” is formed when an anhydronucleoside and a signalling moiety comprising a primary amine are added together in the presence of an activation agent. See page 20, lines 1-2. On page 20, lines 10-11, an “activated anhydronucleoside” is defined as an “anhydronucleoside ready to react with the signalling moiety comprising a primary amine to form a carbamate.” A “modified nucleoside: is formed is defined as a nucleoside covalently modified at the 2’ or 3’ position of the ribose with a signalling moiety. See page 3, lines 11-14.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was “ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing

identifying characteristics sufficient to show that the applicant was in possession of the claim invention.

See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by “whatever characteristics sufficiently distinguish it”).

Applicants’ specification contains drawings, structural chemical formulas, and descriptions of the various starting compounds, intermediate products, and products that sufficiently describe the modified nucleosides made by the methods of the present invention. In addition, in this response, as well as in previous responses to Office Actions, the Applicants have provided Exhibits and the declaration of Dr. Meade to support their belief that the description is sufficient to allow persons of ordinary skill in the art to recognize the scope of what is claimed. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 2-11 and 13-15 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103(a)

Claims 2-11 and 13-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 95/35102 (referred to as Nexstar).

The Nexstar reference discloses methods for making labeled nucleosides from anyhydro-nucleosides having generalized formula 2 in which Z can be an NHR^5 , wherein R^5 can be a fluorescent label. See page 9, line 19, through page 11, line 1. However, there is no disclosure for R^5 being a transition metal chelated by one or more ligands or for R^5 being a metallocene. Moreover, although the process for preparing compounds of formula 2c comprises reacting

compounds of the formula 1c with a metal alkoxide, compounds having formula 2c lack a metal ion. See page 17, line 19, through page 18, line 18.

In contrast, the present invention is directed to making modified nucleosides comprising a metal ion and at least one ligand.

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

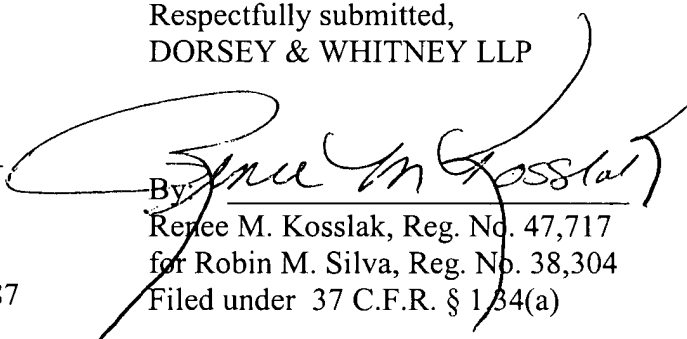
There is no teaching in the Nexstar reference of modified nucleosides comprising a metal ion and at least one ligand. Therefore, the requirement of teaching or suggesting all the claim elements has not been met. Applicant respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,
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